UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,185	07/18/2001	C. Frank Bennett	RTS-0258	1505

7590 01/13/2003

Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	6

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/910,185	Bennett et al

Examiner (First Last)	Art Unit
JANE ZARA	~~1234~~ 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 4-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, and 4-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1,2, 4-20 are pending in the instant application.

Election/Restriction

Applicant's election with traverse of SEQ ID NO: 3 in Paper No.5 is acknowledged. The traversal is on the ground(s) that the various antisense sequences claimed comprise a single invention because they are all subsubsequences of the same target molecule and further that searching all the antisense sequences claimed would not impose an undue burden onto the examiner. This is not found persuasive because each antisense sequence is a distinct and separately patentable invention, despite the fact that all the sequences are subsequences of a single, common target molecule. In addition, searching the appropriate data bases for all of the antisense sequences claimed would present an undue burden on both the examiner and the existing search facilities.

The requirement is still deemed proper and is therefore made FINAL.

The amendment filed on October 15, 2002 in response to the election requirement mailed September 19, 2002 has been acknowledged. Applicant timely traversed the restriction (election) requirement in Paper No. 5 .

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11, line 3, the term "active site" is vague and unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of human glioma-associated oncogene-3 of SEQ ID NO: 3 (GLI-3) comprising the administration of antisense oligonucleotides, does not reasonably provide enablement for compositions and methods for the in vivo inhibition GLI-3 expression or for treating any disease or condition associated with the expression of GLI-3 in an animal comprising the administration of antisense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for inhibiting the expression of GLI-3 in vitro or in vivo, and methods for treating or preventing any disease or condition associated with GLI-3, comprising the administration of antisense oligonucleotides between 8-50 nucleobases which specifically target GLI-3.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to

various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting GLI-3 in vivo, or toward a method of treating or preventing any disease or condition associated with GLI-3 expression in an animal comprising the administration of antisense.

The specification teaches the inhibition of GLI-3 encoded by SEQ ID NO: 3 in vitro comprising the administration of antisense oligonucleotides 8-30 nucleobases in length.

The specification fails to teach the inhibition of GLI-3 expression in any organism, or the treatment or prevention of any and/or all diseases or conditions associated with GLI-3 expression in an organism, comprising the administration of antisense between 8-30 nucleobases which specifically target GLI-3 One skilled in the art would not accept on its face the examples given in the specification of the in vitro targeting and inhibition of GLI-3 using antisense as being correlative or representative of the successful inhibition of GLI-3 expression in an organism, or the successful prevention or treatment of any and/or all diseases or conditions in an organism which are associated with GLI-3 expression comprising the administration of antisense, in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of antisense in treating an organism for any and/or all diseases or conditions associated with a target molecule comprising the administration of antisense. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, prevention or treatment effects provided for any disease or condition associated with a particular target molecule by antisense administered, and specifically regarding expression of nucleic acids encoding GLI-3 of SEQ ID NO: 3.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for inhibiting the expression of GLI-3 in vitro or in vivo, and methods for treating or preventing any disease or condition associated with GLI-3, comprising the administration of antisense

oligonucleotides between 8-50 nucleobases which specifically target GLI-3. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target molecule GLI-3 in vivo whereby the its expression is inhibited in vivo, and further that treatment and/or preventive effects are provided for any and/or all conditions or diseases associated with GLI-3 expression. Since the specification fails to provide any particular guidance for the inhibition of GLI-3 expression in an organism comprising the administration of antisense, and since determination of the factors required such in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Ruppert et al or Kalff-Suske et al, in view of the combination in view of Milner et al and Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotide compounds between 8-30 nucleotides which specifically target and inhibit the expression of human GLI-3 of SEQ ID NO: 3 in vitro, and which oligonucleotides further comprise a phosphorothioate internucleotide linkage modification, a 2'-O-methoxyethyl sugar modification, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Ruppert et al (Document AI, submitted in IDS filed on July 18, 2001, Paper No. 3) teach the polynucleotide sequence encoding GLI-3, of SEQ ID NO: 3 (See entire document, especially figure 2 on page 5410 and the accompanying sequence alignment data).

Kalff-Suske et al (Document AA, submitted in IDS filed on July 18, 2001, Paper No. 3) teach the polynucleotide sequence of GLI-3 encoded by SEQ ID NO: 3, as well as mapping of various mutations throughout GLI-3 polynucleotide sequence and their relationship to various craniofacial and limb anomalies associated with Grieg cephalopolysyndactyly syndrome (See entire document, especially accession number AJ250408 and the accompanying sequence alignment data).

Neither Ruppert nor Kalff-Suske et al do not teach the in vitro inhibition of GLI-3 expression using antisense oligonucleotides between 8-50 nucleobases, nor the incorporation of any modification into the antisense oligonucleotides, nor compositions comprising pharmaceutically acceptable diluents or colloidal dispersion systems.

Milner teaches methods of designing and assessing the ability of various antisense oligonucleotides to target and inhibit the expression of a target nucleic acid of known nucleic acid sequence in vitro (See entire document, especially figure 1 on p 538).

Baracchini et al teach the incorporation of phosphorothioate internucleotide linkages, 2'-O-methoxy ethyl sugar modifications, 5 methyl cytosines and chimeric structures into antisense oligonucleotides for enhancing target binding, cellular uptake and stability of antisense oligonucleotides, as well as compositions comprising antisense oligonucleotides, pharmaceutically acceptable diluents and colloidal dispersion systems (see col. 4-14).

It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of GLI-3 in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases because Milner teaches methods of designing and assessing antisense oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro and both Ruppert and Kalff-Suske et al teach the nucleic acid sequence encoding GLI-3 (of SEQ ID NO: 3). One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-50 nucleobases which best target and inhibit GLI-3 expression in order to study this target molecule's role in various cellular processes craniofacial and limb development because GLI-3's role in development had been taught previously by Kalff-Suske et al and Ruppert et al teach the amplification of GLI-3 in tumors (See Ruppert et al in the abstract and introduction on p. 5408. One of ordinary skill in the art would have been motivated to incorporate various modifications

into antisense such as internucleotide linkage, nucleobase, or sugar modifications, as well as designing chimeric antisense oligonucleotides, because Baracchini had taught previously that such modifications contribute to the stability, cellular uptake and target binding of antisense oligonucleotide compounds. One of ordinary skill in the art therefore would have expected that antisense comprising such modifications would exhibit enhanced stability, cellular uptake and target binding. One of ordinary skill in the art would have been motivated to utilize compositions comprising pharmaceutically acceptable diluents and colloidal dispersion systems, in combination with antisense oligonucleotides, for transfecting target cells because such compositions had been taught previously by Baracchini et al and one would have expected that such compositions would minimize toxic effects of target cells while enhancing cellular uptake of the antisense oligonucleotides. Therefore, the invention has a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Application/Control Number: 09/910,185

Art Unit: 1635

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

December 29, 2002

KAREN LACOURCIERE
PATENT EXAMINER